

**Remarks**

Applicant has canceled claims 1-10 without prejudice to pursuing the claims in one or more continuing applications; as a result claims 1-18 are canceled and claims 19-24 are pending. Claim 19 has been amended to clarify the claim language. No new matter has been added.

**Rejections Under 35 U.S.C. § 112, Second Paragraph**

The Examiner rejected claims 19-24 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicant has amended claim 19 to recite that the step of comparing serves to classify the unknown tissue.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraw the rejection of claims 19-24 under 35 U.S.C. § 112, second paragraph, as indefinite.

**Rejections Under 35 U.S.C. § 102**

The Examiner rejected claims 19, 20 and 23 as anticipated by Rothberg et al. (US 5,871,697; "Rothberg"). Applicant respectfully traverses the rejection.

The Examiner states that Rothberg teaches that the statistical comparison of data from diseased and nondiseased tissues, specifically the "use of an average and standard deviation for each of individual signals to compare and classify tissues" (Office Action at page 3).

Applicant respectfully disagrees with the Examiner's characterization of the use of average and standard deviation values as equivalent to any step in the claimed methods. In particular, Applicant asserts that Rothberg fails to teach or suggest the use of a nonparametric rank ordering of means and of differences between means as is presently claimed.

Rothberg uses a parametric statistical model for interpretation of those individual gene expression variables which distinguish between tissue classes. Thus, Rothberg describes the "significance" between variable values as being defined by how many standard deviations one result is from the mean of a comparison group. That approach is heavily dependent on the accuracy and reproducibility of the absolute scale of variable measurement. For this reason, implementation of the classification method described by Rothberg is not generalizable across experimental settings which use different absolute scales.

Applicant has overcome this limitation by providing a scaleless approach for variable comparison, which uses rank order of means and rank order of differences between means as

primary discriminators between groups. This can readily be embodied in a graphical, scaleless, display such as a ternary plot (as shown and described in the Figures and specification). Furthermore, since discrimination between groups relies on the relative separation between groups, rather than the absolute value of separation, the claimed method is more robust in describing consistent patterns between groups across multiple experimental platforms which differ in their absolute scales.

Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of the claims as anticipated by Rothberg.

The Examiner rejected claims 19-21 and 23 as anticipated by Golub et al. (US 6,647,341; “Golub”). Applicant respectfully traverses the rejection.

The Examiner states that Golub teaches the statistical comparison of data from normal vs. diseased tissues, specifically “gene expression patterns that comprise an average and standard deviation of gene expression values” and that the data is “ranked (e.g., by density)” (Office Action at page 4).

As described above for Rothberg, Golub uses a parametric statistical model for interpretation of those individual gene expression variables which distinguish between tissue classes. Thus, Golub also describes “significance” between variable values as being defined by how many standard deviations one result is from the mean of a comparison group. That approach is not generalizable across experimental settings which use different absolute scales, as described above in connection with Rothberg.

In contrast, Applicant’s method utilizes a scaleless approach for variable comparison, which uses rank order of means and rank order of differences between means as primary discriminators between groups. Since discrimination between groups relies on the relative separation between groups, rather than the absolute value of separation, this approach is more robust in describing consistent patterns between groups across multiple platforms which differ in their absolute scales.

#### **Rejections Under 35 U.S.C. § 103**

The Examiner rejected claims 19-21 and 23-24 as unpatentable over Rothberg et al. (US 5,871,697; “Rothberg”). Applicant respectfully traverses the rejection.

As noted above, Rothberg fails to teach an essential step of the claimed methods, that of ranking the means and differences of the means between the index and the contrast groups. Also as noted above, Rothberg does not suggest this essential step; the teachings of Rothberg are limited to parametric comparisons using standard deviation. This methodology does not suggest to one of ordinary skill in the art the rank-based nonparametric method of Applicant. Due to this deficiency, the teaching of Rothberg is insufficient to provide the basis for a prima facie case of obviousness.

Accordingly, Applicant asserts that Rothberg fails to teach or suggest all of the elements of the claimed invention. Applicant therefore requests that the Examiner withdraw the rejection of claims 19-21 and 23-24 as unpatentable over Rothberg.

The Examiner rejected claim 22 as unpatentable over Rothberg et al. (US 5,871,697; "Rothberg") in view of Suga et al. (US 5,739,808; "Suga"). Applicant respectfully traverses the rejection.

Claim 22 recites a ternary plot display, and Suga is cited for its teaching of same. As for the rejection of the other claims as unpatentable over Rothberg, Applicant respectfully notes that the Rothberg patent is deficient in its teaching of a method that ranks the means and differences of the means between the index and the contrast groups. Due to this deficiency, the teaching of Rothberg is insufficient to provide the basis for a prima facie case of obviousness. Suga does not remedy this deficiency.

Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claim 22 over Rothberg in view of Suga.

### **CONCLUSION**

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. Accordingly, a notice of allowance is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee

occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,  
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